

**[REDACTED] pharmacokinetic  
modelling of intravenous and intranasal  
formulations of naloxone in healthy  
volunteers**

**Internal reference:** IMIMFCTL/NLX\_1

**Development Phase:** Phase I

**NCT number:** NCT06306391

**Protocol Summary**

**(version 3.0, 06<sup>th</sup> February 2024)**

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## **PROTOCOL SUMMARY**

<b>Clinical trial title</b>	<b>[REDACTED] pharmacokinetic modelling of intravenous and intranasal formulations of naloxone in healthy volunteers.</b>
<b>Protocol internal reference</b>	HMRIFCTL/NLX_1
<b>NCT number</b>	NCT06306391
<b>EudraCT number</b>	2023-506064-14-00
<b>Version/date</b>	3.0/06th February 2024
<b>Sponsor identification</b>	[REDACTED]
<b>Request type</b>	<p>Request for authorization of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community.</p> <p>The Investigational Medicinal Product (IMP) to be used in the clinical trial has a marketing authorization in the EU member state concerned.</p>
<b>Principal Investigator (PI)</b>	[REDACTED]
<b>Institution</b>	[REDACTED]
<b>Research Ethics Committee</b>	<p>The clinical protocol will be approved by the Ethics Committee for Drug Research [REDACTED]</p>
<b>Clinical phase</b>	Phase I
<b>Disease or disorder</b>	Healthy volunteers
<b>Inclusion criteria</b>	<ul style="list-style-type: none"><li>• Healthy male or female volunteers according to physical examination, vital signs, ECG and safety laboratory parameters and</li></ul>

	<p>results should be within normal ranges or considered as non-clinically relevant by the investigator.</p> <ul style="list-style-type: none"> <li>• Age <math>\geq 18</math> and <math>\leq 55</math> years.</li> <li>• Body mass index (BMI) <math>\geq 18</math> and <math>\leq 30</math>.</li> <li>• Able/willing to be compliant with the study restrictions.</li> <li>• Able to read Spanish and adhere to study requirements.</li> <li>• Signed informed consent prior to any study-mandated procedure.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Life-time substance use disorders (SUD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).</li> <li>• Consumption of prescribed opiates (in the last 6 months).</li> <li>• Smoking.</li> <li>• History of or ongoing clinically relevant diseases or conditions.</li> <li>• Being under any administrative or legal supervision.</li> <li>• Pregnancy and breastfeeding</li> <li>• Positive blood or urine test for drugs of abuse or alcohol breath test prior to study drug administration.</li> <li>• Life-time history of mental diseases.</li> <li>• History of anxiety or depression not completely recovered within 12 months prior to study drug administration, as assessed by the Dual Diagnosis Screening Interview (DDSI).</li> <li>• Any other clinically relevant disease or condition that in the judgment of the investigator might interfere with the subject's ability to comply with study procedures or requirements and/or bias the interpretation of the study results and/or jeopardize the subject's safety.</li> <li>• Ongoing gastrointestinal diseases or history of gastrointestinal surgery affecting absorption.</li> <li>• Subjects with a clinically significant disease within one month prior to study drug administration.</li> <li>• Any clinically relevant findings in physical examination, vital signs, 12-lead ECG and safety laboratory parameters.</li> <li>• Positive hepatitis or HIV test.</li> <li>• Known hypersensitivity to any drug or drug excipients.</li> <li>• Use of drugs known to induce or inhibit hepatic drug metabolism (e.g., cimetidine) within one month prior to study administration or during the study and use of citrus juice during the study.</li> <li>• Any prescription or over-the-counter (OTC) product including herbal, homeopathic, vitamins, minerals and nutritional supplements within one week prior to study drug administration.</li> <li>• Intake of foods or beverages containing xanthine (more than 5 units of coffee, tea or cola drinks per day).</li> <li>• Donation of blood or plasma within one month prior to study drug administration or transfusion of blood or plasma for medical/surgical reasons or intention to donate blood or plasma within one month after study drug administration.</li> <li>• History of inadequate venous access and/or experience of difficulty donating blood.</li> <li>• Subject included in a clinical study within 3 months prior to study drug administration.</li> </ul>
<b>Study Design</b>	<p>A single-dose, 2-period, 2-sequence, fasting, open label, crossover randomized design, comparing the pharmacokinetics (PK) and</p>

	pharmacodynamics (PD) of intranasal (IN) and intravenous (IV) naloxone solutions
<b>Study Drugs</b>	IV naloxone (Naloxona Kern Pharma 0.4 mg/mL solution for injection and infusion), IN naloxone (Nyxoid 1.8 mg nasal spray solution in single-dose container, Mundipharma Pharmaceuticals, S.L.)
<b>Number of subjects / groups</b>	Approximately 8 healthy male and female subjects will be randomly assigned to one of two sequences in the crossover study. All subjects will receive the same dose of naloxone intranasally or intravenously and the sequence will be determined following randomization.
<b>General Objective</b>	The aim will be to characterize the PK and PD of two formulations of naloxone (intranasal and intravenous) in healthy subjects, which will be used to verify/validate nasal-CNS-PBPK (Physiologically Based Pharmacokinetic) model predictions following intranasal dosing.
<b>Specific objectives:</b>	<p><b>1. Pharmacokinetics objectives:</b>  To calculate plasma PK parameters listed below using a non-compartmental model:</p> <ul style="list-style-type: none"> <li>• Observed maximum concentration: <math>C_{max}</math>.</li> <li>• Observed minimum concentration: <math>C_{last}</math>.</li> <li>• Time to observed maximum concentration: <math>t_{max}</math>.</li> <li>• Time lag (time to first measurable plasma concentration): <math>t_{lag}</math>.</li> <li>• Area under the concentration-time curve (<math>AUC_{0-24h}</math>, <math>AUC_{0-t}</math>, <math>AUC_{0-\infty}</math>) where t is the latest observed timepoint.</li> <li>• Terminal elimination half-life: <math>t_{1/2}</math>.</li> <li>• Apparent clearance: <math>Cl/F</math>.</li> <li>• Apparent volume of distribution: <math>Vd/F</math>.</li> <li>• Elimination rate constant (<math>\lambda_z</math>).</li> </ul> <p><b>2. Pharmacodynamic objectives:</b>  To assess the PD effects of naloxone by measuring:</p> <p><b>2.1. Primary PD endpoints</b>  Effects of naloxone on Heart Rate (HR) and Blood pressure (BP).</p> <p><b>2.2. Secondary PD endpoints</b>  Effects of naloxone on cortisol in plasma (Camí, 1988) on Visit 1 and Visit 4.</p> <p><b>3. Safety objectives</b>  To evaluate drug safety focusing on:</p> <ul style="list-style-type: none"> <li>• Treatment-emergent AEs from Day 1 to end of study (EOS).</li> <li>• Treatment-emergent potentially clinically significant abnormalities (PSCAs) in vital signs, ECG and safety laboratory parameters from Day 1 to EOS.</li> </ul>
<b>Schedule and expected completion date</b>	<p>All adverse events and concomitant medications will be assessed, reviewed and recorded from the informed consent signature to the EOS visit.</p> <p><b>Screening period: Up to 28 days</b>  Following a signed informed consent, subjects will be screened for eligibility. Subjects will undergo a complete demographics, medical history, medication history, physical examination, height, weight, vital</p>

sign evaluation (blood pressure, pulse rate, and body temperature), resting 12-lead ECG, clinical laboratory tests (chemistry, hematology, coagulation profile, urinalysis, HIV, hepatitis B & C diagnostic profile), urine pregnancy test, an alcohol breath test and urine drug screen within 28 days prior to receiving study medication.

**First Treatment period:**

**Visit 1 (Day 1):**

- Subjects will be admitted to the [REDACTED] Research Unit (CRU) on Day 1, after a fasting period of at least 8 hours. All eligibility criteria will be confirmed.
- On Day 1, before study drug dosing, the following assessments will be performed: (i) fasting body weight, (ii) fasting blood collection for clinical safety laboratory tests, (iii) ECG, (iv) vital signs (blood pressure, heart rate, body temperature), (v) physical examination, (vi) urinalysis, (vii) a caffeine test, (viii) an alcohol breath test, (ix) a EtG/EtS urine test, (x) urine drug test (xi) concomitant medications, (xii) urine pregnancy test.
- Each subject will be assigned randomly to one of the sequences.
- Study drug dosing will take place around 08:00 in the morning.

After study drug dosing, the following assessments will be performed ( $\pm$  5 minutes time window if needed at 0.25h and  $\pm$ 10 min for 24 hr. time-point if needed would be acceptable):

- Blood PK sampling
- IN and IV routes: pre-dose, 2min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 35 min, 45 min, 1h, 1.5h, 2h, 4h and 6h.
- Blood PD sampling at pre-dose, 15min, 30min, 1h, 2h, 4h, 6h
- 12-lead ECG pre-dose, 3h, 6h.
- Vital signs (BP, HR and body temperature) at pre-dose, 15min, 30min, 1h, 1.5h, 2h, 4h, 6h post-dose.
- AE will be assessed and reviewed all along the day.
- Subjects will be discharged from the URC on Day 1 in the afternoon unless they present clinically significant drug-related AE impairing daily activities at the time of the discharge.

**Day 2 (24h post-dose)**

- Phone call reviewing adverse events and concomitant medication.

**Wash out period: At least 3 days**

**Second Treatment Period:**

**Visit 2 (Day 4 at least 72h from the first dose):**

- Subjects will be admitted to the CRU. All assessments described in Period 1 will be performed during Period 2.
- Prior to leaving the CRU after Visit 2 procedures, **we initiate the End-of-Study visit (EOS):**

The following assessment will be performed: (i) Body weight (ii) Fasting (4 hours) clinical safety laboratory tests (chemistry, hematology, coagulation profile, urinalysis), (iii) Urine pregnancy test (females only), (iv) alcohol tests and urine drug screen, (v) 12-lead ECG, (vi) vital signs (Blood pressure, Heart Rate, Body temperature), (vi) physical examination, (vii)

	<p>EtG/EtS test, (viii) review of AEs and (ix) concomitant medications.</p> <p><b>Follow-up call (Day 5):</b></p> <ul style="list-style-type: none"> <li>Phone call reviewing adverse events and concomitant medications and confirming overall health status of a subject.</li> </ul> <p><b>This phone call would complete the EOS visit.</b></p>
<b>Expected completion date</b>	This study is expected to last approximately 3 months from the First Subject First Visit to the Last Subject Last Visit.
<b>Duration of subject participation</b>	<p>The total study duration for an individual subject will be between 2 to 6 weeks.</p> <p>All visits will be on an out-patient basis, but Visit 1 and Visit 2 will be long visits (between 7h Visit 1 to 12 h Visit 2) [REDACTED]</p>
[REDACTED]	<p>Naloxone is a semisynthetic morphine derivative and is a specific opioid antagonist that acts competitively at opioid receptors. It reveals very high affinity for the opioid receptor sites. Naloxone does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. In the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity. Naloxone has not been shown to produce tolerance or cause physical or mental dependence.</p> <p>Intranasally administered naloxone has been demonstrated to be rapidly absorbed, as evidenced by very early appearance (as early as 1 minute after administration) of the active substance in systemic circulation. A study investigating intranasal naloxone (Nyxoid™) at doses of 1, 2, 4 mg (MR903-1501) shows that the median (range) tmax associated with intranasal administration of naloxone was 15 (10, 60) minutes for 1 mg, 30 (8, 60) minutes for 2 mg and 15 (10, 60) minutes for 4 mg intranasal doses. Onset of action following intranasal administration can reasonably be expected to occur in each individual before the tmax is reached.</p> <p>The half value duration (HVD) for intranasal administration were longer than for intramuscular administration (intranasal, 2 mg, 1.27h, intramuscular, 0.4 mg, 1.09h) from which we can infer a longer duration of action of naloxone given by the intranasal rather than the intramuscular route.</p> <p>The overall aim is to develop a PBPK model for drug release, disposition and dissolution following intranasal drug delivery. Following delivery, drug release from the formulations and disposition in the nasal cavity will be described. The model will also account for drug transport through epithelial tissue and mucociliary clearance. Predicted local brain and systemic PK will therefore be linked to drug release, dissolution, and disposition in the brain and the rest of the body. In vitro permeability, transporter kinetic and proteomics data from the olfactory region, as well as published clinical data following intravenous and intranasal delivery will be used to support this. Integration of all these processes in a dynamic model will help to disentangle different kinetic</p>

	<p>process which contribute to this complex system, which will help us to explore the interplay between various processes.</p> <ul style="list-style-type: none"> <li>• IN: 1.8 mg nasal spray, solution in single-dose container.</li> <li>• IV: 1 mg in total (from 0.4 mg/mL injectable solution)</li> </ul> <p>Doses selected, in the low range of those tested previously in clinical opioid overdose situations, were already tested experimentally in a bioavailability study in healthy subjects comparing the two routes of administration of naloxone that will be evaluated in this protocol (Tylleskar, 2019).</p>
<b>Statistical methodology</b>	<p>This is a Phase I study to assess the PK and PD of naloxone intranasal vs intravenous administration. Given the nature of this Phase I study, the sample size was not based on power calculations and therefore statistical analyses will be mainly descriptive. Subjects will be randomized in two sequences:</p> <ul style="list-style-type: none"> <li>• Intranasal -&gt; washout period -&gt; intravenous (n=4)</li> <li>• Intravenous -&gt; washout period -&gt; intranasal (n=4)</li> </ul>